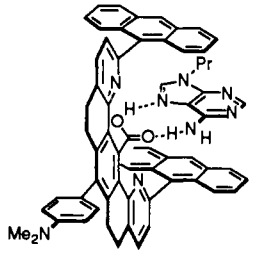
from both analyses were identical, and the association constants agreed within 13%. The association constant thus obtained, K_{assoc} = 25 000 ± 6000 M^{-1}, is the largest reported to date for a complex between a synthetic receptor and a nucleic acid base.[17]

The importance of the carboxylic acid in the complexation is evidenced by the negligible effect that ca. 0.02 M 9-propyladenine has on the ^1H NMR chemical shifts of a 4.5 × 10^{-3} M solution of ester **6**. Lancelot has shown that butyric acid binds 9-ethyladenine in chloroform-*d* (K_{assoc} = 160 M^{-1}) by forming simultaneous hydrogen bonds to N-1 and N-6 and to N-6 and N-7, the former favored by a 2.8:1 ratio.[18] Thus, it is tempting to ascribe



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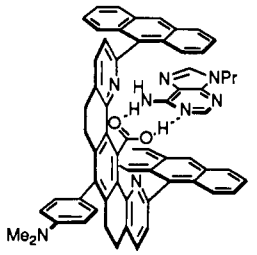
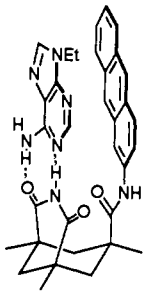


9

the high affinity of **1** for 9-propyladenine to the formation of complexes such as **8** and **9**. The complexation shifts in both host and guest are compatible with the presence of both of these complexes.[17]

While the factors contributing to the stability of the complex remain to be determined, comparison with known receptors is informative. Rebek's receptor **10** uses two hydrogen bonds and a single π-stacking interaction to complex 9-ethyladenine with an association constant of 440 M^{-1}.[3c-f,19] It can be concluded that the second stacking interaction provided by **1** increases its K_{assoc} by approximately 60-fold. More importantly, it has been shown that "π-sandwiching" and hydrogen bonding to a *single* edge of adenine can result in exceptional binding affinity. High



10

binding affinity in other systems requires simultaneous hydrogen bonding to N-1, N-6 (two sites), and N-7.[3c-f,h] Since N-7 and one N-6 site are inaccessible in double-stranded RNA and DNA, the molecular tweezer strategy may better allow for selective binding to these macromolecules. This problem and the complexation of mononucleotides in protic solvents represent challenges toward which our current efforts are directed.

Acknowledgment. Funding from the NIH (GM 38010) and the NSF (CHE 58202) is gratefully acknowledged. Generous contributions toward the NSF-PYI program from the Monsanto, Rohm and Haas, and CIBA-GEIGY companies is acknowledged with gratitude.

(16) Nakano, M.; Nakano, N. I.; Higuchi, T. *J. Phys. Chem.* **1967**, *71*, 3954–3959. For a discussion of the use of this method, see: Conners, K. A. *Binding Constants*; Wiley: New York, 1987; p 197.

(17) Binding study at 298 K. Individual association constants (K_{assoc}) were calculated for each of the three proton resonances monitored in **1**. The nine values obtained from three runs were averaged. $\Delta\delta_{max}$ values for **1** (all upfield shifts): anthracene H-10, 0.60 ppm; anthracene H-4, 0.52 ppm; (dimethylamino)phenyl H-2, 21 Hz. Other protons became obscured during the titration. A 1 × 10^{-3} M solution of 9-propyladenine containing 4 × 10^{-4} M **1** showed the following upfield shifts ($\Delta\delta$): H-2, 0.16 ppm; 4-NH_2, 0.40 ppm; H-8, 0.40 ppm; 9-CH_2, 0.07 ppm.

(18) Determined by ^1H NMR at 303 K: Lancelot, G. *J. Am. Chem. Soc.* **1977**, *99*, 7037–7042.

(19) A related receptor containing two Kemp triacid units uses four hydrogen bonds and one stacking interaction to complex 9-ethyladenine with K_{assoc} = 11 000 M^{-1} (30% $CD_3CN/CDCl_3$, 25 °C), ref 3c-f.

Orderly Functional Group Dyads. Recognition of Biotin and Adenine Derivatives by a New Synthetic Host[1]

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Received May 15, 1989

The catalytic effects of enzymes and the specificity of biogenic receptors illustrate the remarkable properties of properly ordered functional group arrays. The development of general approaches to orderly functional group arrays is an important challenge to the synthetic organic chemist. We describe here a generalizable approach to chiral functional group dyads. The method is illustrated by the preparation of **1** and **2**, chiral molecules wherein two carboxylic acids may intersect at an angle of approximately 120°. The functional groups of these molecules are well-arranged for binding to several guests, including biotin and adenine derivatives, through formation of four hydrogen bonds. Host **1** binds to 9-ethyladenine (**3**) in THF-d_8. Control experiments suggest that **3** interacts with the host through the use of N7 and *both* hydrogen atoms at N6. In $CDCl_3$, host **2** binds very effectively to 9-ethyladenine, to biotin methyl ester (**4**), and to several other guests.

Triple ribonucleic acid helix formation and protein–nucleic acid interactions take advantage of the ability of the adenine base to form four hydrogen bonds (H-bonds).[3] Two H-bonds may be made to N6 and N7 (as in the Hoogsteen nucleic acid dimers), while at the same time another two H-bonds may be made to N6 and N1 (as in the Watson–Crick dimer).[4,5] Cyclic urea derivatives such as biotin methyl ester (**4**) also present two potential sites for hydrogen bond formation. Modeling studies suggested that a single molecule may bind to both sides of adenine or biotin provided that the host molecule contain two properly arranged carboxylic acids that intersect at about a 120° angle.[6,7] The

(1) Part 10 in a series on the Chemistry of Synthetic Receptors and Functional Group Arrays. Part 9: Wilcox, C. S.; Cowart, M. D.; Sucholeiki, I.; Bukownik, R. R.; Lynch, V. In *Proceedings of the 5th International Symposium on Inclusion Phenomena*; Atwood, J., Ed.; Plenum Press: New York, 1989.

(2) Fellow of the Alfred P. Sloan Foundation, 1988–1990.

(3) (a) Seeman, N. C.; Rosenberg, J. M.; Rich, A. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 804–808. (b) Saenger, W. *Principles of Nucleic Acid Structure*; Springer-Verlag: New York, 1984; Chapter 18.

(4) Hoogsteen, K. In *Molecular Associations in Biology*; Pullman, B., Ed.; Academic: New York, 1968; pp 21–38.

(5) Watson, J. D.; Crick, F. H. C. *Nature (London)* **1953**, *171*, 737.

(6) (a) A diimide that binds strongly to adenine derivatives in chloroform has been described: Williams, K.; Askew, B.; Ballester, P.; Buhr, C.; Jeong, K. S.; Jones, S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 1090–1094. (b) A macrocyclic diamide that binds 9-butyladenine in chloroform by simultaneous Watson–Crick–Hoogsteen motifs has been developed: Goswami, S.; Van Engen, D.; Hamilton, A. D. *J. Am. Chem. Soc.* **1989**, *111*, 3425–3426. (We thank Prof. Hamilton for making available a preprint of this manuscript.)

(7) Several crescentic or macrocyclic hosts containing convergent hydrogen bonding sites have been described. Recent contributions include the following: Kelly, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* **1987**, *109*, 6549. Bell, T. W.; Liu, J. *J. Am. Chem. Soc.* **1988**, *110*, 3673. Kilburn, J. D.; MacKenzie, A. R.; Still, W. C. *J. Am. Chem. Soc.* **1988**, *110*, 1307. Pant, N.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 2002. Rebek, J., Jr. *J. Mol. Recognition* **1988**, *1*, 1–8. Osterberg, C. E.; Arif, A. M.; Richmond, T. G. *J. Am. Chem. Soc.* **1988**, *110*, 6903.

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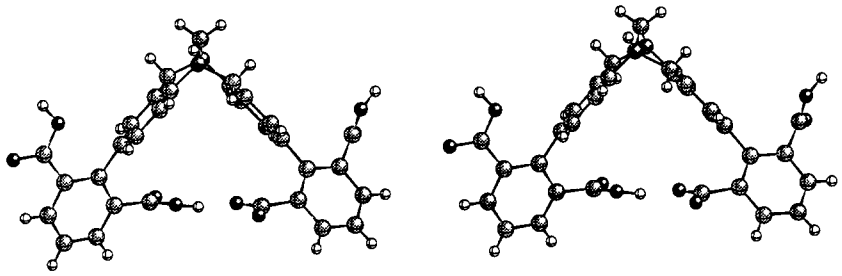


Figure 1. Stereoview of tetraacid 1. Structure determined by single-crystal X-ray diffraction.[17]

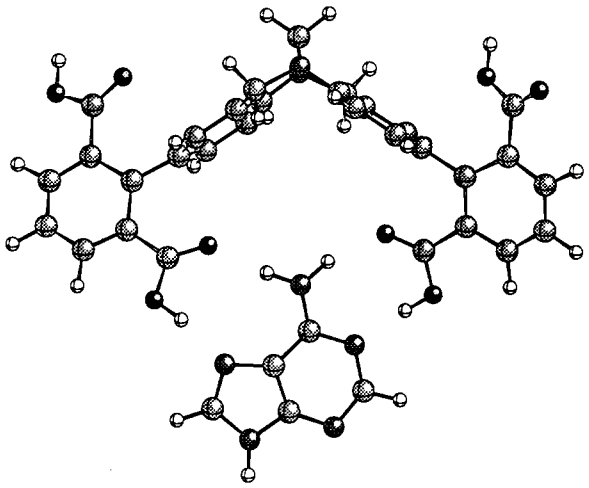
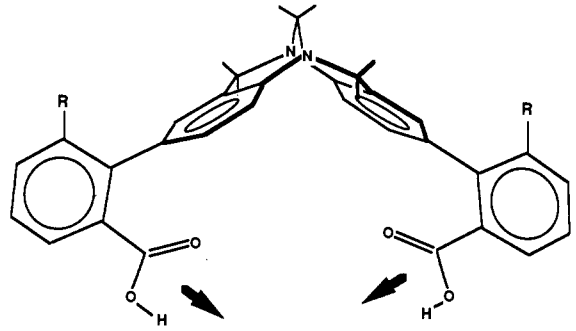
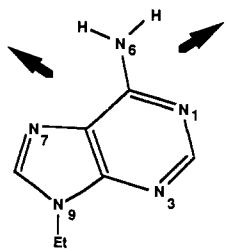


Figure 2. Ball-and-stick illustration of one possible favorable interaction between host 1 and adenine.

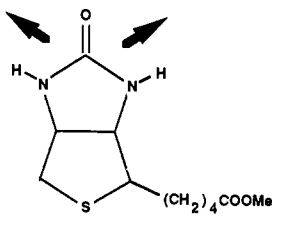
preparation and properties of two hosts (tetraacids 1 and 2) that meet this structural prescript are described here.[8]



1 R = COOH
2 R = H

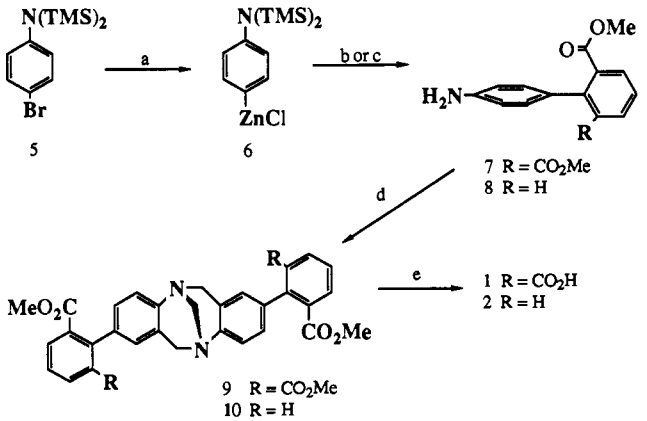


3



4

Scheme I



[a] (a) t-BuLi/Et_2O–THF, then $ZnCl_2$/THF; (b) dimethyl 2-iodoisophthalate and $Ni(PPh_3)_4$/THF, 23 °C; (c) methyl 2-bromobenzoate and $Ni(PPh_3)_4$/THF, 23 °C; (d) H_2CO/HCl/MeOH; (e) LiOH/MeOH/H_2O.

The synthesis of hosts 1 and 2 (Scheme I) incorporates Negishi's powerful approach to unsymmetrical biphenyl derivatives.[9] Halogen–metal exchange with *N,N*-bis(trimethylsilyl)-4-bromoaniline (5) provided the arylzinc halide 6 which was coupled to dimethyl 2-iodoisophthalate to afford the biphenylamine 7 in 20% overall yield or to methyl 2-bromobenzoate to afford biphenylamine 8 in 44% yield. By our usual methods, aniline 7 afforded dibenzodiazocine tetraester 9 in 50% yield.[10] Quantitative saponification of tetraester 9 provided the tetraacid 1 [recrystallized from ethanol/water, mp (decomposition) >300 °C].[11] By a similar pathway, aniline 8 provided diacid 2.

Dynamic NMR investigations of 1 and 9 provided an opportunity to investigate through-space functional group interactions. The experiments revealed, as expected, significant hindrance to rotation about the aryl–aryl bonds[12] (Supplementary Material). The barrier to such rotation in tetraester 9 was found to be 14.5 kcal/mol at the coalescence temperature (37 °C) and was insensitive to solvent. Interestingly, the corresponding process in tetraacid 1 was only slightly different. The barrier for aryl–aryl rotation for the tetra*acid* was 15.0 kcal/mol (at 20 °C) in 50% THF-d_8–$CDCl_3$ and dropped only to 14 kcal/mol in THF-d_8 or methanol-d_4. These observations suggest that an intramolecular H-bond (observed in the solid state, see Figure 1) is weak. This weak interaction leads to slightly diminished rotation rates for the tetraacid in less polar solvents. In polar solvents this intramolecular H-bond is insignificant.

The effects of receptor 1 (0–20 mM) upon the NMR resonances of 9-ethyladenine (2 mM) were examined. Saturation characteristics were easily observed. Host 1 binds quite strongly (K_a

(8) A key structural element in this molecule is the 5,11-methano[*b,f*][1,5]dibenzodiazocine unit. Dibenzodiazocines are easily prepared, rigid, and chiral structural units for macrocyclic and nonmacrocyclic synthetic receptors: (a) Wilcox, C. S. *Tetrahedron Lett.* **1985**, *26*, 5749–5742. (b) Wilcox, C. S.; Greer, L. M.; Lynch, V. *J. Am. Chem. Soc.* **1987**, *109*, 1865–1867. (c) Cowart, M. D.; Sucholeiki, I.; Bukownik, R. R.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 6204–6210. (e) Wilcox, C. S.; Cowart, M. D. *Tetrahedron Lett.* **1986**, *27*, 5563–5566. A discussion of the conformational properties of these molecules is presented in ref 10.

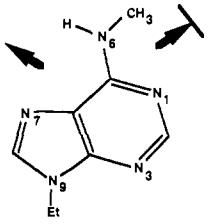
(9) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. Negishi, E.; Takahashi, T.; King, A. O. *Org. Synth.* **1987**, *66*, 67–74.

(10) Sucholeiki, I.; Lynch, V.; Phan, L.; Wilcox, C. S. *J. Org. Chem.* **1988**, *53*, 98–104.

(11) All new compounds were characterized by ^1H NMR, ^{13}C NMR, IR, MS, and elemental analysis.

(12) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; pp 156–179.

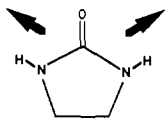
= 140 M^{-1}) to 9-ethyladenine (**3**) in THF-d_8.[13] For comparison, the binding of benzoic acid (K_a = 30 M^{-1}) and 2,6-diphenic acid (K_a = 20 M^{-1}) to **3** in THF-d_8 was also examined. The method of continuous variance (Job plot, Supplementary Material) revealed a 1:1 stoichiometry for the complex.[14-16] The results reveal that the binding of 9-ethyladenine is a unique feature of the orderly diacid. Support for the importance of simultaneous Watson–Crick and Hoogsteen interactions (Figure 2) is provided by the observed stoichiometry and especially by the relatively weak binding of 6-*N*-methyl-9-ethyladenine (**11**, K_a = 14 M^{-1}). This latter molecule cannot form four concurrent hydrogen bonds with the host.



11

Tetrahydrofuran competes for H-bond sites, and association constants should be greater in chloroform than in THF. For example, the K_a for interaction of benzoic acid and 9-ethyladenine is 700 M^{-1} in $CDCl_3$ but only 30 M^{-1} in THF. Host **1** was poorly soluble in chloroform, and therefore host **2** was prepared and found to be easily dissolved in $CDCl_3$.

Host **2** in $CDCl_3$ is an outstanding new host for guests which present two H-bonding surfaces. Association constants for host **2** with several guests: 9-ethyladenine (**3**), 4.5 ± 1.7 × 10^4 M^{-1}; biotin methyl ester (**4**), 1.7 ± 0.3 × 10^4 M^{-1}; 2-imidazolidone (**12**), 2.1 ± 0.4 × 10^4 M^{-1}; trimethyleneurea (**13**), 3.3 ± 1.6 × 10^4 M^{-1}; 2-aminopyrimidine (**14**), 2.6 ± 0.5 × 10^3 M^{-1}.



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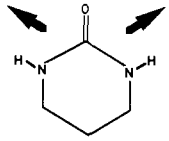
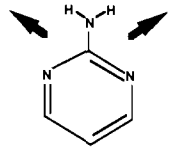


13



14

To further explore solvent effects on host–guest interactions of this type, the affinity of these new hosts for 9-ethyladenine in polar and hydrogen bonding solvents (methanol-d_4 and deuterated aqueous methanol) was examined. In these solvents only proton transfer was observed, and there was no evidence for any association of the components of the resulting salt.[16]

This communication describes a practical approach to molecules that hold two functional groups in an orderly interrelationship. Hosts **1** and **2** contain two carboxylic acids so arranged as to support simultaneous formation of four hydrogen bonds with biotin or adenine derivatives and many similar substrates. This very simple synthesis provides multigram quantities of products and can be easily modified to afford new hosts in which various functional groups are brought into opposition or other orderly configurations. Further investigations of the binding properties and catalytic effects of host **2** and analogous functional group dyads are underway.

Acknowledgment. This work was made possible through funds provided by the National Institute of General Medical Sciences (GM-34846) and from the Alfred P. Sloan Foundation. X-ray structural analysis was carried out under the direction of Jaime E. Abola. Support for the x-ray diffraction laboratory is provided through PHS Grant No. 1-S10-RR02381-01.

Supplementary Material Available: Figure illustrating 300 MHz NMR ($CDCl_3$) spectra of tetraester **9** at 323, 310, and 233 K, Job plot[14] showing the change in concentration of the complex as a function of mole fraction of receptor, and partial crystallographic data including numbering scheme and positional parameters for all atoms of tetraester **9** (7 pages). Ordering information is given on any current masthead page.

Thermal Generation of α,3-Dehydrotoluene from (*Z*)-1,2,4-Heptatrien-6-yne

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Contribution No. 7946, Arnold and Mabel Beckman Laboratories of Chemical Synthesis California Institute of Technology Pasadena, California 91125

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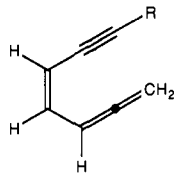
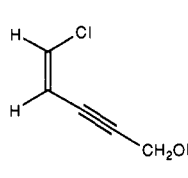
(*Z*)-1,2,4-Heptatrien-6-yne (**1**) undergoes a first-order thermal reaction to produce an intermediate or intermediates whose reactivity is consistent with that of a species designated α,3-dehydrotoluene.



1 R = H
5 R = TMS



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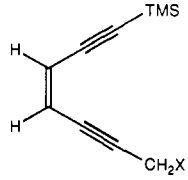
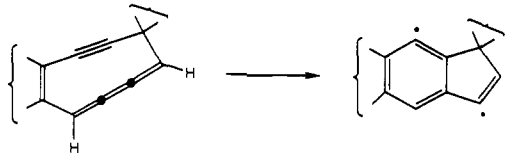


3 X = OH
4 X = $NHNH_2$

Recently, a new class of antitumor antibiotics has been defined on the basis of their proposed transformation to highly reactive, DNA-bound biradical intermediates. In the case of the antibiotics calichemicin and esperamicin, the reactive intermediate is proposed to be a 1,4-dehydrobenzene derivative and is suggested to arise thermally from a (*Z*)-enediyne in a cyclic version of the Bergman reaction.[1,2] Neocarzinostatin chromophore has been proposed to produce a 3,7-dehydroindene derivative through the cyclization reaction depicted in eq 1.[3] The lack of precedent in the latter



(1)

(13) Association constants were determined by direct analysis of NMR or UV/fluorescence titration data. The general procedure and the analytical process are described in ref 8d.

(14) Job, A. *Ann. Chim.* **1928**, *9*, 113. For an outstanding overview of techniques for measuring complex stoichiometry and stability, see: Connors, K. A. *Binding Constants*; Wiley: New York, 1987.

(15) Intermolecular hydrogen bonding of a carboxylic acid to N7/N6 of an adenine derivative has been observed (crystallographic data) to occur in the solid state without proton transfer: Narayanan, P.; Berman, H. M.; Rousseau, R. *J. Am. Chem. Soc.* **1976**, *98*, 8472.

(16) NMR chemical shift changes induced by dilution of an equimolar mixture of **1** and **2** in (deuterated) aqueous methanol were very small and linear, as required for proton transfer phenomena and not association. In contrast, the same experiment in THF-d_8 revealed both large changes in chemical shift and saturation binding characteristics.

(17) The molecule crystallized from ethanol–water as an internal salt. A proton has been transferred from one acid to a diazocine nitrogen. The resulting ammonium group is hydrogen bonded to the carboxylate of a nearby molecule (not shown). This proton transfer does not occur in THF or chloroform.

(1) (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466. (c) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (d) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.

(2) (a) Bergman, R. G.; Jones, R. R. *J. Am. Chem. Soc.* **1972**, *94*, 660. (b) Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082. (c) Lockhart, T. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091. (d) For a definition and discussion of the term "dehydroaromatic", see: Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25.

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